32. (New) An isolated polynucleotide that hybridizes to the coding region of SEQ ID NO:2 or to the complement of the coding region of SEQ ID NO:2 under stringent hybridization conditions of 50% formamide, 5x SSC, 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, 50 μg/ml salmon sperm DNA, 0.1% SDS, and 10% dextran sulfate at 42°C, and wash conditions of 0.2x SSC and 50% formamide at 55°C, followed by 0.1x SSC with EDTA at 55°C, wherein the complement of said polynucleotide detects, by microarray analysis, a polynucleotide that is differentially expressed by at least about 1.8-fold in an in vivo or in vitro cardiac disease model.

33. (New) The polynucleotide of claim 32, wherein said polynucleotide encodes a polypeptide having at least 90% sequence identity with the polypeptide of SEQ ID NO:1.

REMARKS

Claims 1-8 are pending and under prosecution. Applicants have amended claims 1-6 and 8 and added new claims 30-33 to further clarify the invention. The amendments to claims 1-6 and 8 are supported in the specification, for example, on page 12, lines 14-17; page 49, lines 27-31; page 16, line 30, through page 17, line 3; page 17, lines 4-11; page 21, line 8, through page 24, line 13; pages 57-63, Example 1; pages 70-72, Example 8; and page 74, lines 21-25.

Support for new claim 30 is found in the specification, for example, on page 12, lines 14-18. Support for new claim 31 is found in the specification, for example, on page 7, lines 22-26, and in Figure 2. Support for new claim 32 is found in the specification, for example, on page 13, lines 19-25. Support for new claim 33 is found in the specification, for example, on page 12, lines 14-18. No new matter is added by any of the foregoing amendments.

I Objection to Drawings

The Examiner objected to Figure 2 under 37 C.F.R. § 1.84(g). Applicants have submitted with this amendment a corrected Figure 2 (now Figures 2A and 2B) that complies with the formal requirements of 37 C.F.R. § 1.84(g). Withdrawal of this objection is respectfully requested.

II. Rejection of Claims 1-8 Under 35 U.S.C. § 101

The Examiner rejected claims 1-8 under 35 U.S.C. § 101 on the grounds that "the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility." (Office Action, page 3.) Because the Examiner has failed to establish a prima facie case of lack of utility, this rejection is respectfully traversed.

To reject a claimed invention under 35 U.S.C. § 101, the Examiner must establish a prima facie showing that the claimed invention lacks a specific and substantial utility. M.P.E.P., 8th ed., § 2107.02, pp. 2100-40, 41. Applicants respectfully submit that the Examiner has not provided sufficient evidentiary support to establish a prima facie showing. The Examiner stated that "at the present time, clone P00210_D09 cannot be used . . . because there is no biological activity known for the protein." (Office Action, page 4.) This assertion, however, does not preclude a specific and substantial utility for the claimed invention. Even if the biological function of the encoded protein is unknown, which Applicants do not concede, the Utility Examination Guidelines state that "the utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have a specific and substantial utility because, e.g., it hybridizes near a disease-associated gene or it has gene regulating activity." 66 Fed. Reg. at 1095. Here, the claimed polynucleotides serve as useful probes or markers for specific diseases, independent of the function of the encoded polypeptides. Therefore, the Examiner's reliance on the encoded polypeptides to establish a specific and substantial utility does not provide sufficient support for the instant rejection.

The Examiner further stated that "there is no information provided that suggests that P00210_D09 could be used as a diagnostic before the onset of disease." (Office Action, page 4.) Applicants submit that there is no support for the Examiner's position that a diagnostic agent must operate before the onset of disease in order to be useful. Certainly, agents that diagnose disease during or after its onset or that monitor disease progression have substantial utility. The disclosed in vivo myocardial infarction model supports such a utility for the claimed polynucleotides. Thus, the unfounded allegation that the claimed invention lacks utility because it does not predict the onset of disease fails to support the instant rejection.

Notwithstanding Applicants' belief that the Office has not met its burden, and solely in the interests of expediting prosecution, Applicants will nonetheless respond to the Examiner's assertion that the invention lacks a specific and substantial utility. Applicants submit that the

specification sets forth numerous specific and substantial utilities for the polynucleotides of the claimed invention. For example, the specification provides that "genes that are differentially expressed in subjects suffering from a disease, such as cardiac, renal or inflammatory disease, . . . are useful targets for intervention to diagnose, prevent, or treat such diseases." (Specification, page 1.) The specification further teaches that the claimed polynucleotide sequences show differential expression by microarray analysis in an in vivo model for myocardial infarction. (Specification, pages 28-31.) The specification also provides that the polynucleotides of the invention are useful as probes and primers for nucleic acid amplification procedures for "detecting and diagnosing a disease, specifically cardiac, kidney, or inflammatory disease." (Specification, paragraph bridging pages 42-43.) Therefore, the claimed polynucleotide sequences are useful, for example, as probes or markers for the diagnosis of myocardial infarction. This utility is specific because it relates to the particular polynucleotide sequences of the invention and not to all polynucleotide sequences in general. This utility is also substantial because it has a "real world" application in the diagnosis of a particular disease state.

In addition to the invention's utility in myocardial infarction diagnosis, the specification sets forth other specific and substantial utilities for the claimed polynucleotides. For example, Applicants teach that P00210_D09 mRNA (SEQ ID NO:2) demonstrated significantly decreased expression in response to growth-factor induced cardiac hypertrophy, thus supporting a role for this sequence as "a downstream mediator of known factors that induce cardiac hypertrophy." (Specification, page 74.) These data thus support a specific and substantial utility for the claimed polynucleotides and their encoded polypeptides as drug targets for the treatment of cardiac hypertrophy.

The U.S.P.T.O. Utility Examination Guidelines provide that "a rejection based on lack of utility should not be maintained if an asserted utility for the claimed invention would be considered specific, substantial, and credible by a person of ordinary skill in the art in view of all the evidence of record." 66 Fed. Reg. 1092, 1098 col. 3 (Jan. 5, 2001). Applicants need not establish an asserted utility by proof "beyond a reasonable doubt." The standard set forth by the USPTO's Utility Examination Training Materials (available at http://www.uspto.gov/web /offices/pac/dapp/oppd/utility.htm) requires only that the evidence of record, when considered as a whole, would lead "a person of ordinary skill in the art to conclude that the asserted utility is *more likely than not true*. (Emphasis in original.) Here, the evidence of record meets this

standard. At the time of Applicant's invention, those of ordinary skill in the art understood that differentially expressed genes identified by microarray analysis are useful as diagnostic markers and drug targets for specific diseases. For example, the specification cites Heller *et al.*, Proc. Natl. Acad. Sci. USA 94:2150-55 (1997), as teaching the identification of inflammatory-specific genes using microarray analysis. (Specification, page 2, and Heller *et al.*, attached, at page 2155, col. 1 ¶ 3, and paragraph bridging cols. 1-2.) Applicants have also enclosed an abstract from Schena, Bioessays 18:427-31(1996), describing differential gene expression analysis using microarray technology as useful in various applications, including "human disease diagnostics."

Applicants' disclosure further supports that the asserted utilities are more likely than not specific, substantial, and credible to one of ordinary skill in the art. The disclosed model systems for myocardial infarction and cardiac hypertrophy provide a suitable and accepted means in the art for studying cardiac-related diseases. One of ordinary skill in the art would consider the ~2-fold increase in expression of the claimed polynucleotides in the myocardial infarction model as a significant and reliable diagnostic marker, given that the sensitivity of microarray analysis allows accurate detection of expression levels differing by ~2-fold. (Specification, page 24, citing Schena *et al.*, Proc. Natl Acad. Sci USA 93:10614-19 (1996), attached, at page 10618, col. 2, ¶ 5.) One of ordinary skill in the art would further recognize that the predominantly cardiac-specific expression of the claimed polynucleotides supports the asserted utility in cardiac disease diagnosis. (Specification, page 75, lines 2-5, and Figure 5.) Taken together, these facts establish that it is more likely than not that the asserted utility in cardiac disease diagnosis is specific, substantial, and credible to one of ordinary skill in the art.

Applicants further note that the Utility Examination Training Materials state that "*any* reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a specific utility." (Emphasis in original.) Additional, and possibly better, uses for the claimed polynucleotide sequences may well be discovered upon further experimentation and research. However, this possibility does not negate the currently known specific and substantial utilities.

In view of the foregoing arguments, Applicants respectfully submit that the invention of claims 1-8 has at least one specific and substantial utility. Therefore, the rejection of these claims under 35 U.S.C. § 101 may be properly withdrawn. Withdrawal of this rejection is respectfully requested.

III. Rejection of Claims 1-8 Under 35 U.S.C. § 112, ¶ 1 (Enablement)

The Examiner rejected claims 1-8 under 35 U.S.C. § 112, ¶ 1, in conjunction with the foregoing rejection under 35 U.S.C. § 101. Specifically, the Examiner asserted that one of skill would not know how to use the claimed invention because it is not supported by a specific and substantial utility. Applicants respectfully submit that the arguments presented above establish that the claimed invention is supported by a specific and substantial utility. Therefore, one of skill in the art would know how to use the invention under 35 U.S.C. § 112, ¶ 1.

The Examiner further stated that "even if the specification were enabling of how to use the P00210_D09 [the polynucleotide encoding SEQ ID NO:1], enablement would not be found commensurate in scope with the claims." (Office Action, page 6.) Specifically, the Examiner asserted that the specification does not enable claims directed toward "polynucleotides that encode a polypeptide that is at least 80%% [sic] identical to the polypeptide of SEQ ID NO:1, or polynucleotide [sic] hybridizing under stringent conditions to the polynucleotide of SEQ ID NO:2." Applicants have amended claim 1 to recite "a polynucleotide encoding a polypeptide having at least 90% sequence identity with SEQ ID NO:1" or to specific regions thereof. One of ordinary skill in the art would reasonably conclude that a polynucleotide encoding a polypeptide with 90% identity to SEQ ID NO:1 shares a common utility with a polynucleotide encoding SEQ ID NO:1 itself. This conclusion is based on the fact that polynucleotides encoding highly similar polypeptides share significant sequence identity and are more likely than not useful for the same purpose. Applicants have also amended claim 1 to recite a polynucleotide whose complement "detects, by microanalysis, a polynucleotide that is differentially expressed by at least about 1.8-fold in an in vivo or in vitro cardiac disease model." One of ordinary skill in the art would reasonably conclude that any polynucleotide possessing this limitation would have a specific and substantial utility, for example, as a diagnostic marker or probe for myocardial infarction. Therefore, any polynucleotide species that falls within the scope of claim 1 possesses at least one specific and substantial utility, and one of ordinary skill in the art would know how to use such a polynucleotide. Therefore, the specification enables the full scope of claim 1 and dependent claims 2-8, and the rejection of claims 1-8 under 35 U.S.C. § 112, ¶ 1 is overcome.

Because amended claim 1 no longer recites "a polynucleotide hybridizing under stringent conditions with . . . SEQ ID NO:2," the rejection of claims 1-8 under 35 U.S.C. § 112, ¶ 1, is

overcome to the extent that it is based on this subject matter. New claim 32 embraces this subject matter and further recites a hybridizing polynucleotide whose complement "detects, by microanalysis, a polynucleotide that is differentially expressed by at least about 1.8-fold in an in vivo or in vitro cardiac disease model." Therefore, the polynucleotide of claim 32 has utility based on this limitation and on its high degree of identity to SEQ ID NO:2, as would be expected of a polynucleotide that hybridizes under the recited conditions of high stringency.

As the specification teaches how to use the invention commensurate with the scope of claims 1-8, the rejection of claims 1-8 under 35 U.S.C. 112, ¶ 1, may be properly withdrawn. Withdrawal of this rejection is respectfully requested.

IV. Rejection of Claims 1 and 5-8 Under 35 U.S.C. 112, ¶ 1 (New Matter)

The Examiner rejected claims 1 and 5-8 under 35 U.S.C. 112, ¶ 1, on the grounds that recitation of "80%" sequence identity in the claims constituted "new matter," because the specification only recites sequence identities of 75%, 85%, 90%, and 95%. Applicants respectfully remind the Examiner that subject matter present in the originally filed specification, drawings, *and claims* cannot constitute new matter. (See M.P.E.P., 8th ed., §§ 608.04 and 608.04(a), pp. 600-107,108.) Only amendments that alter the originally filed specification, drawings, and claims may introduce new matter. The "80%" figure was present in the originally filed claims and therefore cannot constitute new matter. Notwithstanding the fact that "80%" is not new matter, Applicants have, for other reasons, amended "80%" to "90%," which is fully supported by the specification as originally filed.

V. Rejection of Claims 1 and 5-8 Under 35 U.S.C. § 112, ¶ 1 (Written Description)

The Examiner rejected claims 1 and 5-8 under the written description requirement of 35 U.S.C. § 112, ¶ 1. Specifically, the Examiner asserted that the claimed polynucleotides, some of which encode fragments and variants of SEQ ID NO:1, were not adequately supported by "the instant disclosure of a single polypeptide, that of SEQ ID NO:1 with no known specific activities." (Office Action, paragraph bridging pages 6-7.) Applicants submit that the claims as amended are fully supported by the single representative polynucleotide species of SEQ ID NO:2.

The USPTO's Written Description Guidelines state that an applicant may satisfy the written description requirement "by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention." 66 Fed. Reg. 1099, 1104 col. 3 (Jan. 5, 2001). When an applicant claims a genus, "[s]atisfactory disclosure of a 'representative number' [of species] depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." *Id.* at 1106 col. 3. Here, claim 1 recites polynucleotides with a common feature, that is, the ability to detect, by microarray analysis, a polynucleotide that is differentially expressed by at least about 1.8-fold in an in vivo or in vitro cardiac disease model. Although Applicants disclose only a single representative species (SEQ ID NO:2) having this feature, this species is adequate to demonstrate that Applicants were in possession of a genus of polynucleotides having this particular feature.

As the Examiner stated, claim 1 recites specific regions and variants of the polypeptide SEQ ID NO:1. These regions and variants define the boundaries of the claimed polynucleotides. However, these regions and variants need not share a common structural or functional feature to satisfy the written description requirement, because the genus of claimed polynucleotides already possesses a common feature in detecting differential gene expression. This feature is independent of the function of the encoded polypeptide regions and variants. Therefore, claim 1 complies with the written description requirement of 35 U.S.C. § 112, ¶ 1, as do claims 5-8, which depend from claim 1.

In view of the amendments to claims 1 and 5-8 and the foregoing arguments, Applicants respectfully submit that the rejection of claims 1 and 5-8 under 35 U.S.C. § 112, ¶ 1, is overcome. Withdrawal of this rejection is respectfully requested.

VI. Rejection of Claims 1-8 Under 35 U.S.C. § 112, ¶ 2

The Examiner rejected claims 1-8 under 35 U.S.C. § 112, ¶ 2, on the grounds that the term "stringent conditions" is indefinite. Claim 1(d) as amended no longer recites this term. New claim 32 embraces the subject matter of the prior claim 1(d) and further recites specific hybridization conditions. Therefore, claim 32 is clear and definite, and the rejection of claim 1 under 35 U.S.C. § 112, ¶ 2, is overcome. Withdrawal of this rejection is respectfully requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and an early action to that effect is respectfully solicited. If any issues remain or require further clarification, the Examiner is respectfully requested to call Applicant's counsel at the number below to resolve such issues promptly.

Applicants believe that no fee is due with this amendment. However, if the U.S.P.T.O. determines that a fee is due, please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: July 22, 2002

By: _____

Ginger R. Dreger
Registration No. 33,055
Attorney of Record
620 Newport Center Drive
Sixteenth Floor
Newport Beach, CA 92660
(415) 954-4114

Version with Markings To Show Changes Made

In the specification:

Paragraph appearing at page 7, lines 22-26:

Figures 2A and 2B show [Figure 2 shows] the nucleotide sequence of the clone P00210_D09 (SEQ ID NO:2), in alignment with the encoded amino acid sequence[, where the initiating methionine is circled]. The total length of this sequence is 1031 bases, and the sequence encoded by the open reading frame (275 amino acid polypeptide, SEQ ID NO:1) is bracketed [in the Figure]. The complementary strand is also depicted (SEQ ID NO:19).

Paragraph appearing at page 64, lines 15-16:

Figures 2A and 2B show [Figure 2 (SEQ ID NO:2) shows] the nucleotide sequence of the clone P00210_D09 (SEQ ID NO:2). The total length of this sequence is 1031 bases.

In the claims:

1. (Twice amended) An isolated nucleic acid molecule comprising a poly- or oligonucleotide selected from the group consisting of:

(a) a polynucleotide encoding a polypeptide having at least 90% sequence identity with SEQ ID NO:1, wherein the complement of said polynucleotide detects, by microarray analysis, a polynucleotide that is differentially expressed by at least about 1.8-fold in an in vivo or in vitro cardiac disease model;

(b)[(a)] a polynucleotide encoding a polypeptide having at least [about] 90[80]% sequence identity with amino acids 22 to 122 of SEQ ID NO:1, wherein the complement of said polynucleotide detects, by microarray analysis, a polynucleotide that is differentially expressed by at least about 1.8-fold in an in vivo or in vitro cardiac disease model;

(c)[(b)] a polynucleotide encoding a polypeptide having at least [about] 90[80]% sequence identity with amino acids 56 to 122 of SEQ ID NO:1, wherein the complement of said polynucleotide detects, by microarray analysis, a polynucleotide that is differentially expressed by at least about 1.8-fold in an in vivo or in vitro cardiac disease model;

(d)[(c)] a polynucleotide encoding amino acids 22 to 275 of SEQ ID NO:1, or a transmembrane domain deleted or inactivated variant thereof, wherein the complement of said polynucleotide detects, by microarray analysis, a polynucleotide that is differentially expressed by at least about 1.8-fold in an in vivo or in vitro cardiac disease model;

[(d) a polynucleotide hybridizing under stringent conditions with the complement of the coding region of SEQ ID NO:2, and encoding a polypeptide having at least one biological activity of the polypeptide encoded by clone P00210_D09 (SEQ ID NO:2);]

(e) a polynucleotide encoding at least about 50 contiguous amino acids from amino acids 22 to 122 of SEQ ID NO:1, wherein the complement of said polynucleotide detects, by microarray analysis, a polynucleotide that is differentially expressed by at least about 1.8-fold in an in vivo or in vitro cardiac disease model [encodes a polypeptide having at least one biological activity of the polypeptide encoded by clone P00210_D09 (SEQ ID NO:2)];

(f) a polynucleotide encoding at least about 50 contiguous amino acids from amino acids 56 to 122 of SEQ ID NO:1, wherein the complement of said polynucleotide detects, by microarray analysis, a polynucleotide that is differentially expressed by at least about 1.8-fold in an in vivo or in vitro cardiac disease model [encodes a polypeptide having at least one biological activity of the polypeptide encoded by clone P00210_D09 (SEQ ID NO:2)]; and

[(g) a polynucleotide of SEQ ID NO:2; and]

(g)[(h)] the complement of a polynucleotide of (a) - (f)[(g)].

2. (Once amended) The polynucleotide of claim 1 encoding a polypeptide comprising amino acids 22 to 122 of SEQ ID NO:1, wherein the complement of said polynucleotide detects, by microarray analysis, a polynucleotide that is differentially expressed by at least about 1.8-fold in an in vivo or in vitro cardiac disease model.

3. (Once amended) The polynucleotide of claim 1 encoding a polypeptide comprising amino acids 56 to 122 of SEQ ID NO:1, wherein the complement of said polynucleotide detects a polynucleotide that is differentially expressed by at least about 1.8-fold in an in vivo or in vitro cardiac disease model subjected to microarray analysis.

4. (Once amended) The polynucleotide of claim 1 encoding a polypeptide comprising the sequence of SEQ ID NO:1[2], wherein the complement of said polynucleotide detects, by microarray analysis, a polynucleotide that is differentially expressed by at least about 1.8-fold in an in vivo or in vitro cardiac disease model.

5. (Once amended) A vector comprising [and capable of expressing] a poly- or oligonucleotide of claim 1.

6. (Once amended) A recombinant host cell transformed with a nucleic acid molecule comprising a poly- or oligonucleotide of claim 1.

7. (Reiterated) A recombinant host cell transformed with the vector of claim 5.

8. (Once amended) A method for producing a polypeptide comprising culturing a recombinant host cell transformed with a nucleic acid molecule comprising a polynucleotide [any of the polynucleotides] of claim 1[(a)-(g)] under conditions such that the polypeptide is expressed, and isolating the polypeptide.

30. (New) An isolated polynucleotide encoding a polypeptide comprising a native mammalian homologue having at least 90% amino acid sequence identity to SEQ ID NO:1, wherein the complement of said polynucleotide detects, by microarray analysis, a polynucleotide that is differentially expressed by at least about 1.8-fold in an in vivo or in vitro cardiac disease model.

31. (New) An isolated polynucleotide comprising SEQ ID NO:2 or the coding region of SEQ ID NO:2.

32. (New) An isolated polynucleotide that hybridizes to the coding region of SEQ ID NO:2 or to the complement of the coding region of SEQ ID NO:2 under stringent hybridization conditions of 50% formamide, 5x SSC, 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, 50 μg/ml salmon sperm DNA, 0.1% SDS, and 10% dextran sulfate at 42°C, and wash conditions of 0.2x SSC and 50% formamide at 55°C, followed by 0.1x SSC with EDTA at 55°C, wherein the complement of said polynucleotide detects, by microarray analysis, a polynucleotide that is differentially expressed by at least about 1.8-fold in an in vivo or in vitro cardiac disease model.

33. (New) The polynucleotide of claim 32, wherein said polynucleotide encodes a polypeptide having at least 90% sequence identity with the polypeptide of SEQ ID NO:1.